TREATMENT OF CANCER BY MANIPULATION OF COMMENSAL MICROFLORA

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims the priority benefit of U.S. Provisional Patent Application 62/169,112, filed Jun. 1, 2015, and U.S. Provisional Patent Application 62/248,741, filed Oct. 30, 2015, each of which is incorporated by reference in its entirety.

FIELD

Provided herein are methods of treatment and/or prevention of cancer by manipulation of commensal microflora. In particular, the amount, identity, presence, and/or ratio of microflora (e.g., gut microflora) in a subject is manipulated to facilitate one or more co-treatments.

BACKGROUND

Harnessing the host immune system constitutes a promising approach for the treatment of cancer because of its potential to specifically target tumor cells while limiting harm to normal tissue, with durability of benefit associated with immunologic memory. Enthusiasm has been fueled by recent clinical success, particularly with antibodies that block immune inhibitory pathways, specifically CTLA-4 and the PD-1/PD-L1 axis (Hodi et al. The New England journal of medicine 363, 711-723 (2010); Hamid et al. The New England journal of medicine 369, 134-144 (2013); herein incorporated by reference in their entireties). Early data have indicated that clinical responses to these immunotherapies are more frequent in patients who show evidence of an endogenous T cell response ongoing in the tumor microenvironment at baseline (Tumeh et al. Nature 515, 568-571 (2014); Spranger et al. Science translational medicine 5, 200ra116 (2013); Ji et al. Cancer immunology, immunotherapy: CII 61, 1019-1031 (2012); Gajewski et al. Cancer journal 16, 399-403 (2010); herein incorporated by reference in their entireties). Despite the functional and clinical importance of this T cell-inflamed tumor microenvironment, the mechanisms that govern the presence or absence of this phenotype have not been well understood. Theoretical sources of inter-patient heterogeneity include germline genetic differences at the level of the host, variability in patterns of somatic alterations in tumor cells, and environmental differences with the potential to impact on systemic immunity.

SUMMARY

Provided herein are methods of treatment and/or prevention of cancer by manipulation of commensal microflora. In particular, the amount, identity, presence, and/or ratio of microflora (e.g., gut microflora) in a subject is manipulated to facilitate one or more co-treatments.

In some embodiments, provided herein are methods of treating or preventing cancer in a subject, comprising modulating levels of one or more commensal microbes within the subject to: (A) enhance an immune response by the subject, (B) inhibit the growth or spread of the cancer, (C) inhibit immune evasion by the cancer, and/or (D) enhance the efficacy of a therapeutic. In some embodiments, the levels of one or more commensal microbes are modulated within the gut of the subject. In some embodiments, modulating the levels of one or more commensal microbes comprises increasing and/or decreasing levels of one or more bacterial selected from the genera *Adlercreutzia, Oscillopira, Mollicutes, Butyrivibrio, Bacteroides, Clostridium, Fusobacterium, Eubacterium, Ruminococcus, Peptococcus, Peptostreptococcus, Bifidobacterium, Rikenella, Alistipes, Marinilabilia, Anaerostipes, Escherichia*, and/or *Lactobacillus*.

In some embodiments, modulating the levels of one or more commensal microbes comprises administering a beneficial microbes to the subject. In some embodiments, the beneficial microbes are bacteria. In some embodiments, the bacteria are selected from the genera *Adlercreutzia, Oscillopira, Mollicutes, Butyrivibrio, Bacteroides, Clostridium, Fusobacterium, Eubacterium, Ruminococcus, Peptococcus, Peptostreptococcus, Bifidobacterium, Rikenella, Alistipes, Marinilabilia, Anaerostipes, Escherichia*, and/or *Lactobacillus*. In some embodiments, the bacteria are *Bifidobacterium*. In some embodiments, the *Bifidobacterium* include bacteria selected from the group consisting of *Bifidobacterium lactis, Bifidobacterium bifidium, Bifidobacterium longum, Bifidobacterium animalis, Bifidobacterium breve, Bifidobacterium infantis, Bifidobacterium catenulatum, Bifidobacterium pseudocatenulatum, Bifidobacterium adolescentis*, and *Bifidobacterium angulatum*. In some embodiments, the beneficial microbes are administered as a probiotic composition or via microflora transplant from a donor.

In some embodiments, modulating the levels of one or more commensal microbes comprises administering one or more antimicrobials. In some embodiments, the antimicrobial kills detrimental microbes. In some embodiments, the antimicrobial is an antibiotic. In some embodiments, methods further comprise administration of beneficial microbes to the subject.

In some embodiments, methods further comprise administering to the subject a cancer therapy. In some embodiments, wherein the modulating levels of one or more commensal microbes within the subject enhances an immune response by the subject and/or inhibits immune evasion by the cancer, and the cancer therapy is an immunotherapy. In some embodiments, the immunotherapy comprises administration of anti-CTLA-4 antibodies and/or anti-PD-L1 or anti-PD-1 antibodies. In some embodiments, wherein the modulating levels of one or more commensal microbes within the subject enhance the efficacy of a therapeutic, and the cancer therapy is said therapeutic. In some embodiments, the therapeutic comprises a chemotherapeutic. In some embodiments, methods further comprise testing the subject for immune evasion by the cancer. In some embodiments, methods further comprise surgical, radiation, and/or chemotherapeutic cancer intervention.

In some embodiments, provided herein are kits or compositions comprising a beneficial commensal microbe and a cancer therapeutic, said compositions or components of said kits formulated for therapeutic delivery to a subject.

In some embodiments, provided herein are beneficial commensal microbes for use as a medicament in the treatment of cancer and/or inhibition of immune evasion.

In some embodiments, provided herein are methods of treating or preventing cancer in a subject comprising administering to the subject bacterial formulation comprising bacteria of the genera *Bifidobacterium, Rikenella, Alistipes, Marinilabilia*, or *Anaerostipes*. In some embodiments, at least 50% of the bacteria in the bacterial formulation are of the genera *Bifidobacterium, Rikenella, Alistipes, Marinil-*